This draft guidance document has been prepared to provide information to institutions and others for use in reviewing and investigating allegations of research misconduct involving clinical trials and clinical research. Research institutions, scientific societies and associations, and interested members of the public are invited to submit their comments. Please send all comments to ORI at 5515 Security Lane, Suite 700, Rockville, MD 20852 or by E-mail to: beaton@osophs.dhhs.gov.

Office of Research Integrity

Guidelines for Assessing Possible Research Misconduct in Clinical Research and Clinical Trials

I. Introduction

Clinical research is conducted in a variety of settings ranging from small studies performed at single institutions to large multi-center clinical trials conducted by a consortium of institutions and managed by a coordinating center. Much of this clinical research is supported by the Public Health Service (PHS). The responsible organization (usually the institution where the alleged misconduct occurred) initiates an inquiry or investigation into the allegations which will require the full cooperation of the institution, coordinating center, funding agency, and the Office of Research Integrity (ORI).[1,2] In responding to the allegations, the investigating organization must assess the following issues:

- the need for and availability of resources to investigate and resolve allegations of research misconduct expeditiously

- the need to coordinate human subject protection with the institutional review board (IRB)
- the need to obtain the cooperation and assistance of the coordinating center in conducting an investigation at one site of a multi-center trial and in correcting the data base for an ongoing trial

[1] ORI is part of the Office of Public Health and Science (OPHS), under the Assistant Secretary for Health in the Department of Health and Human Services (DHHS) (see ORI's Internet Site at http://ori.hhs.gov). The DHHS regulations on research misconduct require an institution to notify ORI if it determines at any stage of an inquiry or investigation that there is an immediate public health hazard [see 42 C.F.R. § 50.104(b)(1)]. ORI staff can be directly contacted at 301-443-5330 (ORI's Division of Investigative Oversight) to obtain telephone or on-site advice under ORI's program of Rapid Response for Technical Assistance (RRTA).

[2] ORI will notify the appropriate PHS funding component in all cases. The institution must also notify directly the appropriate PHS funding component if required by the component's clinical trial monitoring unit.

- the need to inform those physicians and patients who rely on the results of the clinical research when significant public health issues arise

- the need to inform the data and safety monitoring committee staff and funding agency personnel who will decide, with the involved institutions, how the questioned clinical data will be handled in analyses and publications
- the need to notify the journal(s) when results of published trials that impact medical practice are seriously questioned

- the need to coordinate the investigational efforts with the Office of Human Research Protections (OHRP) and the Food and Drug Administration (FDA), if appropriate.

II. Purpose

ORI developed these guidelines to assist officials in assessing and investigating possible research misconduct in clinical research and clinical trials involving PHS support or applications for PHS support. They address procedures and problems that are unique to cases associated with research involving human subjects. Therefore, ORI suggests that these guidelines be used as a supplement to the *ORI Model Procedures for Responding to Allegations of Research misconduct* (available at Internet Site http://ori.hhs.gov/html/misconduct/investigation.asp).[3,4]

III. Definitions

Clinical Research is research involving people having or suspected of having a clinical disease (Meinert, C.L., *Clinical Trials Dictionary,* The Johns Hopkins Center for Clinical Trials, 1996) and appropriate control subjects. Clinical research also may include trials in healthy people aimed at disease prevention.

Clinical Trial is a controlled experiment involving the administration of different study treatments in a parallel treatment design to a defined set of study subjects (and controls) for a given disease or related health condition and done to evaluate the efficacy and safety of a test treatment in ameliorating or curing that disease or related health condition. Any such experiment, including those involving healthy people, is undertaken to assess the efficacy or safety of a treatment (e.g.,

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[3] These Guidelines do not establish any legal rights or causes of action by or against individual whistleblowers, respondents, institutions, or others or against the U.S. Department of Health and Human Services or any of its components, representatives, or employees. If any provision of these Guidelines is inconsistent with established rules and regulations under the PHS Act or other Federal laws, the latter will prevail.

[4] The *Standards for Clinical Research* within the NIH Intramural Research Program (available at Internet Site (http://www.cc.nih.gov/ccc/clinicalresearch/standards.html) provides information regarding the conduct of clinical research.

usefulness of monitoring fetal heart rate on pregnancy outcome; usefulness of different dietary schemes in the prevention of hypertension) (*Ibid*.).

Data and Safety Monitoring Committee is a committee of qualified professionals that monitors the accumulating data on safety and study endpoints or results at specified intervals and recommends whether the study should be continued.

Discrepant Data are data that have been identified as questionable by a complainant (*a.k.a.* "whistleblower") or investigating body or that appear to be suspect on the basis of various tests (see Section VII). The discrepancy need not be limited to quantitative research "data" such as measurements of blood pressure.[5]

Inquiry means information gathering and initial fact-finding to determine whether an allegation or apparent instance of scientific misconduct warrants an investigation (42 C.F.R. §50.102).

Institutional Official is the person at the institution who is responsible for assessing allegations of research misconduct and determining whether the allegations warrant inquiries and for overseeing any inquiries and investigations.

Investigation means the formal examination and evaluation of all relevant facts to determine whether scientific misconduct has occurred (42 C.F.R. §50.102). The investigation also determines the extent and significance of the misconduct and who was responsible.

Quality Assurance Audit is a process to evaluate the accuracy of data obtained during a study and, in the case of multi center trials, submitted to the coordinating center for inclusion in the study's data base. The audit is intended to verify investigator compliance with protocol and regulatory requirements, including the obtaining of informed consent. It is also intended to enable institutional, cooperative study, and funding institute staff to evaluate the elements of good clinical practice related to regulatory compliance, data collection, accuracy, and management.[6]

Research Record means, but is not limited to, any data, document, computer file, computer diskette, or any other written or non-written account or object that reasonably may be expected to provide evidence or information regarding the proposed, conducted, or reported research that

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[5] For instance, in a multi-center trial where all examiners are required to be "certified" by the coordinating center, the study forms may falsely report that a certified individual performed the reported test, observation, or evaluation when, in fact, it was performed by a non-certified individual.

[6] Although the findings of an audit may establish an apparent instance of misconduct that warrants an investigation and obviate the need for a formal inquiry, an audit does not fulfill the objectives of and requirement for an investigation under the PHS regulations.

constitutes the subject of an allegation of research misconduct. A research record includes, but is not limited to, grant or contract applications, whether funded or unfunded; grant or contract progress and other reports; laboratory notebooks; notes; correspondence; videos; photographs; X-ray film; slides; biological materials; computer files and printouts; manuscripts, reviewers' comments, and publications; equipment use logs; laboratory procurement records; animal facility records; human and animal subject protocols; Institutional Review Board records; consent forms; medical charts; patient research files, etc.

Research misconduct, **scientific misconduct, or misconduct in science** for PHS means fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting or reporting research. It does not include honest error or honest differences in interpretations or judgments of data. If this definition, which is currently in the PHS regulations at 42 C.F.R. §50.102, is amended by subsequent statute or regulation, the new definition will apply.[7] Institutions may have internal definitions that are more comprehensive than the PHS definition.

Source Data include all information in original documents, records, or certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents, as original records or certified copies (FDA Guidance for Industry, *Computerized Systems Used in Clinical Trials*, April, 1999).[8]

Source Documents are original documents and records including, but not limited to, hospital records, clinic and office charts, laboratory notes, memoranda, subjects' diaries, eligibility checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays and other diagnostic images, subject files, and records kept at the pharmacy, laboratories, and at medico-technical departments involved in the clinical trial (Ibid.).

IV. Regulations and Authority

Individual institutions have primary responsibility for evaluating and responding to allegations of research misconduct when PHS funds or applications for funds are involved (42 C.F.R. §50.101). ORI provides monitoring and oversight to ensure that applicant and awardee institutions comply with the PHS regulations for dealing with allegations of research misconduct and that their

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[7] The Office of Science and Technology Policy has published a new government-wide definition, which is available at Internet Site http://ori.dhhs.gov/html/misconduct/regulation.asp. This definition will not apply to PHS grantee institutions until after it is implemented through revised HHS regulations on research misconduct.

[8] Available at Internet Site http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.htm

resolution adequately protects PHS funds, the integrity of PHS-supported research, and the public. ORI may provide technical assistance to an institution during its inquiry or investigation.

Alternatively, ORI may request that the Department of Health and Human Services (DHHS) Office of Inspector General (OIG) conduct a direct investigation in circumstances when the institution cannot or will not investigate, or if it is determined to be in the public interest.

V. Persons Who May Be Responsible for Committing Misconduct in Clinical Research

In assessing allegations of possible falsification or fabrication of clinical research data, the person responsible for the discrepancies that prompted the inquiry or investigation may not be immediately identifiable. Any member of the research team, regardless of position or level of contribution, from the principal investigator to the technical staff member, administrative data collector, or outside contractor, may be responsible for research misconduct.[9] Thus, all members of the clinical research team should be considered possible respondents (persons under inquiry or investigation), and a major component of the investigation will be identifying who was responsible for any falsification or fabrication that is found.

VI. Sources of Information

Study Protocol and Manuals

A formal written protocol is the basis of any clinical research study or clinical trial. The protocol provides a highly codified set of requirements addressing all aspects of the proposed study: background; subject eligibility and exclusion criteria; data to be collected, reportable events, endpoint; mechanism of data storage, retrieval, statistical analyses and reporting; and identification of the principal and associate investigators. The protocol must be adhered to in the conduct of the proposed clinical research, with deviations permitted only when necessary to ensure patient safety. Before assessing allegations of possible research misconduct in any clinical trial, the persons responsible for the assessment should obtain a copy of the clinical research protocol and develop a thorough knowledge and understanding of the protocol.

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[9] For example, the principal investigator might instruct staff to falsify or fabricate test values on submitted data forms and to falsify documents (e.g., laboratory reports) that support the falsified data. Study coordinators (i.e., nurses or other health care professionals responsible for patient recruitment and randomization and data reporting) might falsify and fabricate data in research records submitted to the coordinating center. Research misconduct also might be committed by physicians or health care professionals responsible for performing tests or evaluations required by study protocol, who report falsified or fabricated data directly in the patient research file or to the study coordinators. Pharmacists might falsify drug accountability records. In summary, anyone associated with the research who has motive or intent may be responsible for falsifying or fabricating clinical research data.

Medical and Other Records

The patient medical chart or file represents the primary source of data for all clinical research, and the research file should state those data accurately. Clinical data are unique in that many documents contained in medical records or documents separate from the medical record are generated by individuals and laboratories independent of the primary investigator and research team. Therefore, much of the research data can be verified from sources outside the control of the investigators or data collectors. These data include nurse and intern/resident notes, consultant evaluations, operative reports, pharmacy records, and records maintained by diagnostic facilities (i.e., clinical laboratories, radiology and pathology departments, etc.). Diagnostic facilities often maintain their own records separate from the copies provided in the patient charts. Billing records also are valuable for establishing the dates of examinations and tests, thereby verifying the procedures performed. Thus, the medical chart and ancillary documents provide unique sources for independent verification of information entered on the research data forms that are used in the analysis of a clinical research study. In some cases the institution may need, in consultation with its IRB, to contact the research subjects. Any of these avenues may be explored to verify data.

Study Personnel

The clinical research team usually involves ancillary personnel who aid the participating physicians in seeing patients, evaluating efficacy and adverse events, conducting diagnostic tests, maintaining research records, and recording data pertinent to analysis of the clinical trial. These personnel include research nurses, floor or office nurses, data management personnel, clinical research coordinators, pharmacists, laboratory personnel, and financial or administrative record keepers. During the inquiry or investigation, identify and interview each staff member who may have relevant information, and determine the role of each person in the collecting, evaluating, and recording of clinical research data.

VII. Identification of Discrepant Data

Assess fully discrepant data in a data base or on clinical research data forms. Without a complete assessment, the individual identifying these discrepancies cannot be certain as to whether the questioned data are the result of error or intentional falsification or fabrication. Many instances of discrepant data are not the result of intentional misconduct. Nevertheless, examine all cases of discrepant data for the possibility that intentional misconduct occurred.

Discrepant clinical research data may be identified as the result of:

- a whistleblower who is a member of the clinical study team recognizing a pattern of

discrepant data, observing another team member recording falsified or fabricated data, or being instructed by a superior to falsify or fabricate data

- a review and comparison of data by clinical site personnel or coordinating center personnel

- a routine quality assurance audit of patient medical files and research records

Statistical methodologies also are useful in identifying discrepant data in clinical research.[10] These techniques include:

- looking for features, patterns, or trends in the data that are "surprising" in the sense that they would be unlikely to occur in usual clinical practice or as a result of the treatment prescribed by the study protocol (unusual recruitment rate patterns, patients adhering perfectly to visit schedules, randomization in chronological order, deletion of outliers, implausible data, abnormally high or low error rates or data queries within centers, and unexpected clinical patterns in data).

- looking for digit preference, where some digits are recorded more frequently than others. The most commonly preferred digits are 0, 5, and even digits.[11] Note that digit preference is normally expected for some manually measured variables (i.e. blood pressure).

- measuring the variability of the data. A smaller than expected variability may be indicative of data manipulation done to reduce the data variability and improve the calculated significance of the results. For multi-center studies, variability measures can be compared to detect centers with extreme variability measures.[12]

VIII. Reporting and Assessment of Data Discrepancies as Possible Intentional Data Falsification or Fabrication

Once discrepant research data are identified, report the matter to the official responsible for receiving and assessing research misconduct allegations at the institution. All institutions applying for or receiving PHS research funding are required to appoint such an official. The institutional official determines whether the occurrence may constitute possible research misconduct (this

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[10] Evans, S. Statistical aspects of the detection of fraud. In S. Lock and F. Wells (Editors), Fraud and misconduct in medical research, London, BMJ, Publishers, 1993, pp. 61-74.

[11] Stem and leaf plots are useful tools for examining digit preference.

[12] For normally distributed data the obvious measure of variability is the *variance*. For non-normally distributed data, useful measures of variability would be the *range* (useful for detecting the absence of outliers) and the *interquartile range* (this approach may be more informative than the range as it is not strongly influenced by outlying data).

process is called a pre-inquiry assessment).[13] The institutional official, or individuals delegated by the official to perform the assessment, will examine the discrepant information with respect to the type and number of discrepancies, evidence of possible document alteration or fabrication, and the context within which the discrepancies occurred.

The individuals doing the assessment should apply objective standards to evaluate whether inadvertent errors were the cause of the discrepancies in the records.[14,15] Certain types of data discrepancies suggest possible intentional data falsification or fabrication, as opposed to honest error or carelessness. Examples include:

- presence of two copies of a document that appear identical except that the test result, date, or patient name or other identifiers on the two documents differ

- a document that is internally inconsistent, e.g., records of prescribed and administered drug dosages do not agree

- a document for which an original matching document cannot be found in the patient's medical record

- copies of documents that appear to be altered (e.g., a "halo" around the date or test value that may indicate that the original date or value has been obliterated with opaque correction fluid), and an original matching document cannot be found
- documents where patient interview responses are reported in the research records, but contact between interviewer and patient is not documented or verifiable in the patient's medical file or in other available records (e.g., telephone records, billing records, appointment schedules, etc.)

- documents with fabricated dates or test data so that, while the reported data fit the protocol requirements, the results do not appear to be reasonable or attainable (e.g., a report that a much higher than expected proportion of patient visits occurred in the last few

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[13] The staff of the project or the data coordinating center do not perform this function. They must bring problems to the attention of the institutional official, who handles the pre-inquiry assessment. Even if the matter is eventually determined not to meet the criteria for possible research misconduct, the official also may be the appropriate individual to assess other forms of misconduct or poor management and to resolve the issue.

[14] ORI staff are available to consult on the standards required to determine inadvertent error and on the selection of appropriate individuals to assist in assessing the discrepant records. In the case of possible research misconduct in a clinical trial, ORI may be helpful in advising the institution whether a data audit or an immediate inquiry or investigation is required.

[15] Nearly all of the large cases of research misconduct in clinical research were first identified during an audit. In many of these circumstances the discrepant data were initially attributed to inadvertent error or sloppiness rather than research misconduct. Auditors often do not recognize the clues to possible misconduct, since they are charged with validating the data and confirming records to support the reported items of data, rather than with detection of research misconduct.

days of the protocol suggests that some of the visits may never have taken place or may have occurred after the time window had closed).

If the discrepancies can clearly be determined to have resulted from inadvertent error, it may be possible to resolve the matter at the pre-inquiry assessment stage and close the case without a formal inquiry. In that circumstance, the institutional official should document the reasoning and evidence for the decision.

IX. Notifications to ORI and PHS Agencies

If the pre-inquiry assessment indicates that misconduct in clinical research may have occurred, a formal inquiry or investigation is warranted (Section X below), and ORI should be notified immediately to ensure that all necessary procedures are followed and that appropriate officials are informed. In some instances, for example those involving immediate public health hazards, ORI must be informed of potentially problematic situations.[16,17] Regardless of the outcome of the pre-inquiry assessment, ORI must be notified if ORI previously contacted the institution regarding the allegation. Initial notification to ORI may be accomplished effectively by a telephone call involving ORI staff and officials from the institution (clinical research site) and the PHS funding component.

If it is determined that a data audit is necessary (as a prelude to or as part of the inquiry or investigation process), an ORI staff member may attend the audit to provide technical assistance for identifying and documenting instances of possibly falsified or fabricated data. ORI can provide advice on what to look for during an audit that might suggest intentional misconduct. ORI can also advise officials on how to request additional information without prematurely alerting the study staff about possible misconduct.

Clinical research, by virtue of the involvement of human subjects, is governed by supplemental DHHS regulations, which include:

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[16] ORI is responsible for general oversight and information management for the PHS about questions of possible research misconduct and for alerting or briefing appropriate PHS staff about these matters, frequently to explain the reasons that a matter does *not* meet the criteria of research misconduct.

[17] The institution is responsible for notifying ORI if it ascertains *at any stage* of the inquiry or investigation that any of the following conditions exist (42 C.F.R. § 50.104(b)):

(1) There is an immediate health hazard involved;
(2) There is an immediate need to protect Federal funds or equipment;
(3) There is an immediate need to protect the interests of the person(s) making the allegations or of the individual(s) who is the subject of the allegations as well as his/her coinvestigators and associates, if any;
(4) It is probable that the alleged incident is going to be reported publicly;
(5) There is a reasonable indication of possible criminal violation. In that instance, the institution must inform ORI within 24 hours of obtaining that information. ORI will immediately notify the Office of Inspector General.

- 45 C.F.R. Part 46, "Protection of Human Subjects" (OHRP)
- 21 C.F.R. Part 312, "FDA New Drug, Antibiotic and Biologic Product Regulations"
- 21 C.F.R. Parts 812 and 813, "FDA Investigational Medical Device Regulations."
- 21 C.F.R. Parts 50 and 56, "Protection of Human Subjects" (FDA) and "Institutional Review Boards" (FDA), respectively.

In appropriate circumstances, the institution must ensure that the Office for Human Research Protections (OHRP)[18] or the FDA office overseeing the regulated product[19] is notified, either by the institution or by ORI.

When institutional officials decide to initiate an inquiry or investigation of clinical research, they should notify ORI immediately and follow established institutional procedures for conducting an inquiry. If the inquiry process determines that a formal investigation is warranted, the institution must notify ORI and provide ORI with the institutional inquiry report. ORI notifies the appropriate funding program within PHS. When ORI directly requests that an institution conduct an inquiry, the resulting inquiry or investigation report must be sent to ORI, regardless of the case's outcome.

There have been many ORI cases where the initial notification and subsequent assessment of the evidence were followed by an audit (or follow-up information was obtained by coordinating center staff) that revealed a reasonable explanation other than research misconduct for the questioned data. These instances have ranged from a case where ORI had reason to believe a patient rather than a staff member was responsible for falsifying a medical record to a case where data collectors misunderstood how to calculate or record test results. In these cases, ORI proceeds no further than offering its advice and closes its file after reviewing the information collected by the data coordinating center.

Additional Considerations for Allegations of Research Misconduct Involving Multi-Center Clinical Trials

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[18] Office for Human Research Protections (OHRP), OPHS, DHHS, has regulatory information and advice available at Internet Site http://ohrp.osophs.dhhs.gov/.

[19] The Food and Drug Administration (FDA) Center for Drug Evaluation and Research's regulatory information is available at Internet Site http://www.fda.gov/cder/regulatory.

In a multi-center trial, participating institutions do not function independently.[20] Multi-center clinical trials sponsored by PHS generally require submission of patient data from each center to a data coordinating center at regular intervals during the study.[21] Independent laboratory facilities and reading centers also may provide additional vital study information obtained from biological sample analyses, X-ray and imaging assessments, or other tests.

If a formal inquiry or investigation is warranted, ORI can provide assistance to the participating institutions and to the coordinating center staff and facilitate cooperation among them.

X. Conducting the Formal Inquiry and Investigation

The purpose of an *inquiry* is to determine if further investigation into the allegations is warranted. The inquiry phase in clinical cases is often limited to confirmation that there are unresolved discrepancies in data that may be the result of falsification or fabrication. The inquiry committee may consist of one or more individuals charged with evaluating the allegation. The committee should interview the respondent (the individual against whom the allegation of research misconduct was made), if one is identified. The committee generally interviews the complainant (the individual who made the allegation) and other individuals with knowledge about the study. An inquiry is not exhaustive and makes no determination as to whether research misconduct occurred. However, if a respondent makes an admission of research misconduct at the inquiry stage, it should be documented and reported to ORI.[22]

If the inquiry confirms the presence of unexplained data discrepancies that may be the result of falsification or fabrication, the institution should immediately open an *investigation* to determine the scope of the discrepancies, to find evidence that supports either a finding of honest error or one of falsification or fabrication, and to identify the responsible individual(s). The institution should

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[20] Most large multi-center trials are coordinated by a group at one location and are governed by a formal study protocol and a fairly extensive manual of operations. The manual provides detailed instructions for implementing the protocol. Many multi-center clinical trial studies provide formal instruction courses and meetings to ensure that participating personnel at each center are informed of study parameters and know the correct method for submitting data to the coordinating center. Some training sessions devote attention to research misconduct topics, specifically what research misconduct is, how to detect it, and what to do if research misconduct is suspected. Participating personnel are kept apprised of additions or alterations to the study protocol and reporting requirements through formal protocol amendments.

[21] A data and safety monitoring committee usually monitors the accumulating data on safety and study endpoints at specified intervals and recommends whether the study should be continued. The data safety and monitoring committee also decides how missing or "suspect" data are to be assessed in overall analyses of the study.

[22] See Internet Site at http://ori.dhhs.gov/html/publications/guidelines.asp, ORI Model Procedures, p. 32: "Recording Admissions," or at http://ori.dhhs.gov/html/misconduct/inquiry_issues.asp, "Confessions and Negotiated Pleas."

notify ORI if it has not already done so. The investigation committee generally consists of at least three members with appropriate expertise. The committee should interview the respondent, complainant, and other individuals with knowledge of the alleged research misconduct, with the interviews recorded and transcribed. The committee should also examine all relevant facts, sequestered evidence, records, and data in an effort to determine whether research misconduct has occurred.

Evidence

When discrepant data are detected, institutional officials should *immediately secure all original* documents related to the matter in question. This action "freezes" these original records, so that they are not altered, destroyed, or augmented. The potential success of an inquiry or investigation into possible research misconduct in clinical research hinges on acting quickly to document and secure all evidence pertinent to the allegation(s). If the records are not secured immediately, an investigation may be compromised and the allegations may be unresolvable.[23] An *inventory of the sequestered materials* should be prepared at the time of their sequestration.

Documents that should be secured in a clinical trial or clinical research study that is under investigation include:

- inpatient hospital charts (records of hospitalization), including all laboratory and diagnostic tests performed and their results

- outpatient clinic or physician office records of patient visits, including all laboratory and diagnostic tests performed and their results

- all research records relevant to the clinical study or trial, including research charts and files (records or data forms completed for research purposes) in written, computerized, and electronic form, reports of special laboratory tests performed solely for research purposes, and reports obtained from outside physicians and laboratories

- grant applications and progress reports for the study, and all versions of manuscripts derived from the study.

Obtain data forms and other documents or specimens submitted to the data coordinating center, central laboratories, or reading centers and compare them with the primary medical records and other source documents maintained at the participating center. The cooperation and assistance of the data coordinating center personnel are essential for a complete examination of questioned

[23] For example, in one case, staff from a PHS funding institute notified the participating clinical site in a multi-center trial that a team would visit the site with the intention of reviewing questionable data derived from a specific patient. Upon arriving, the team discovered that the dated report in question, which had been copied during a previous audit, had disappeared, and the file report copy was now undated. The disappearance or alteration of evidence could have been avoided if appropriate procedures had been followed.

records. Audit checklists prepared by the data coordinating center (e.g., a summary of patient eligibility, treatment, toxicity, and follow-up status reported to the coordinating center and incorporated within the coordinating center data base) represent an invaluable resource for assessing suspect data. For a sample of an audit checklist, see Attachment 1.

Patient medical records are subject to state laws and statutes regarding access. Review of these records by PHS employees and reviewers for the clinical trial's coordinating center generally is granted when the patient consents to participate in PHS-funded research. The review of medical records is authorized by the regulations governing the award of the Federal grant or contract.

Because original medical records generally cannot be removed from the hospital, clinic, or physician's office, advance plans must be made for on-site examination of the records. Since information in the medical records may be essential for the patient's ongoing medical care, copies of sequestered medical records must be made available to the patient's medical care providers. Thus, securing patient records as evidence can be a cumbersome and intrusive process requiring the cooperation of hospital administrative staff, medical records departments, staff physicians, and other medical personnel.

Photocopies of evidence related to data discrepancies that may be due to research misconduct should be made for off-site analysis and documentation of possible data falsification or fabrication. Pair each copied source document with an Evidence Record Sheet, annotated to describe the source of the copied document and discrepancies with other records. For a sample Evidence Record Sheet, see Attachment 2.

In clinical research cases, take special care when maintaining investigational files to guard the privacy of participating subjects. ORI recommends that investigating staff prepare a redacted set of records to be used for investigational purposes and analyses. In the redacted records, identify subjects only by a number (preferably the assigned study number), with all subject names and other associated identifiers removed. Keep a second set of record copies with subject names in secure evidence files during the investigation or oversight to protect patient confidentiality. This set may be destroyed after DHHS has taken final action.

XI. Preparing the Inquiry/Investigation Report

Instructions and examples for preparing inquiry and investigation reports are provided in the *ORI Model Procedures for Responding to Allegations of Scientific Misconduct* (available at ORI's Internet Site http://ori.hhs.gov/html/misconduct/investigation.asp).

Additional considerations for reporting on clinical research or clinical trials are:

Framing Allegations as Issues:

- Describe how the original discrepancies in the clinical research data that prompted the investigation were identified.

- Frame all allegations as PHS issues of research misconduct (e.g., that Respondent falsified/fabricated the results [or date] of the chest X-ray for the eligibility check list, falsely reporting that there was no evidence of possible cancer)

Institutional Investigation:

- Process

  Identify all members of the clinical research team and state whether each person was interviewed. Identify relevant evidence and research records.

- Findings

  For each issue, compare the discrepant research data or information reported on the study research form(s) or other reports to those data recorded in the original hospital, clinic, or other available medical records of the patients.

  For each issue, identify each data discrepancy for each subject. An issue may involve similar data discrepancies associated with several patients, such as falsification of a test result to make the subjects appear to meet the eligibility requirements when they do not (see, for example, Attachment 3).

  For each issue, state the investigation committee's conclusion, endorsed by the institution official as to whether the respondent committed research misconduct.

- Attachments:

  Append to the investigation report copies of all significant documentary evidence (with patient identifiers redacted) that is referenced in the report (e.g., copies of discrepant study forms, original medical records, research records, etc.). The inclusion of appropriate summary tables (with patient names redacted) is recommended.

XII. Conclusion

These ORI Guidelines are recommendations to institutions for assessing possible research misconduct involving clinical research and clinical trials. Because every clinical case has a possible or perceived impact on public health, ORI should be contacted and consulted early in the process

of an institution's response to possible research misconduct in clinical settings.[24] ORI recognizes that allegations of possible research misconduct are unpleasant for all concerned. We hope that this guidance will assist institutions in responding appropriately.

XIII. Attachments

Attachment 1	Audit Checklist Sample
Attachment 2	Instructions - Evidence Records
Attachment 3	Sample Summaries of Investigation Findings

ORI/DIO 1/8/01

[24] Call ORI's Division of Investigative Oversight (301-443-5330) for telephone or on-site advice under ORI's Rapid Response for Technical Assistance (RRTA); see Internet http://ori.hhs.gov/html/programs/orioffersrapidresponse.asp.

Attachment 1

Audit Checklist Sample

Attachment 1

Institutional Site Visit Audit

Auditor(s) _____

Protocol – Study Number – Name –

Institution –

Eligibility Status – Eligible

Item	Record	Confirmed	Institutional Record
********* ENTRY RELATED DATA *********			
Date of birth	10/ 30/ 52	[___]	_____
Date of signed consent	Not recorded	[___]	_____
Date of randomization	2/ 13/ 97	[___]	_____
Date of biopsy	1/ 7/ 97	[___]	_____
Type of biopsy	Excisional	[___]	_____
Date of surgery	1/ 9/ 97	[___]	_____
Date of axillary dissection	1/ 9/ 97	[___]	_____
Max. clinical tumor size	2.5 cm	[___]	_____
Estrogen receptor value	0.0 fmol/mg	[___]	_____
Number of positive nodes	4	[___]	_____
Pre-entry bilirubin	0.4 mg %	[___]	_____
Pre-entry platelets	262.0 k/cu mm	[___]	_____
Pre-entry serum creatinine	0.9 mg %	[___]	_____
Pre-entry SGOT	21.0 I.U./ml	[___]	_____
Pre-entry white blood count	8.8 k/cu mm	[___]	_____
********* TREATMENT RELATED DATA ******			
Date of first treatment	2/ 13/ 97	[___]	_____
Treatment assigned		[___]	_____
Grade 4 or 5 toxicity reported	No	[___]	_____
********* FOLLOW-UP RELATED DATA ******			
Date of last follow-up	3/ 21/ 00	[___]	_____
Method of last follow-up	Seen by MD;Inst rpt.	[___]	_____
Disease Status	Alive, with T/F	[___]	_____
Date of recurrence	8/ 3/ 99	[___]	_____
Date of second primary	N/A	[___]	_____
Date of death	3/ 21/ 00	[___]	_____

Other Comments: _____

Attachment 2

Instructions--Evidence Records

Attachment 2

INSTRUCTIONS--EVIDENCE RECORDS

For each data item that appears to be falsified or fabricated, obtain copies of the following to document the false claim:

1. The data form page that reports the false data item (and additional pages if needed to identify who entered the false information).

2. The document that establishes the true data (e.g., lab report, X-ray report, physician note, etc.).

3. Any altered document prepared to support the false claim.

For each of the above items, prepare an "Evidence Record" sheet (see sample attached):

1. Fill in the protocol number and the subject identification number.

2. Identify the document type (e.g., lab report, physician progress note, history and physical, X-ray report, etc.)

3. Identify the source of the document (e.g., hospital chart, clinic chart, physician office chart, research file, or directly from a hospital/clinic department file (radiology department, pathology, clinical lab, ECG lab, etc.)

4. Indicate whether the document from which you made the copy was the original or a photocopy or carbon copy.

5. Indicate if there are any evident alterations to the document from which you made the copy: write-overs, opaque correction fluid (e.g. White Out), etc. If opaque correction fluid has been used, indicate what is written over the correction and what is written under the corrected area, if possible.

Note other changes to the document (e.g., information written in a different pen or different handwriting from rest of document, original typing on a photocopy, photocopied signature on document with original typing, etc.).

Instructions - Evidence Records (continued)

To prepare the copy:

1. For each source document copied, remove the subject's name and social security number either before copying (with removable Post-It Correction or Cover Up Tape) or after copying (with black marker).

2. Staple "Evidence Record" sheet to copy of document.

Original records:

1. Hold the original records to protect their authenticity.

EVIDENCE RECORD

1. Protocol Number_____ Subject ID_____

2. Document Type_____

3. Source of Document_____

4. Document copied from is: original document_____

   photocopy_____

   carbon copy_____

5. Evident Alterations:

   Overwrite_____

   Information overwritten changed:

   from_____

   to_____

   Opaque correction fluid (e.g., White Out)_____

   Information changed:

   from (under correction)_____

   to: (over correction)_____

   Other changes:_____

   _____

Attachment 3

Sample Summaries of Investigation Findings

Attachment 3

SAMPLE SUMMARIES OF INVESTIGATION FINDINGS

Allegation	PHS Issue	Inv. Comm. Determination	Institutional Decision
Estrogen receptor status of Pt X was misrepresented in publication ____	that Respondent falsified the estrogen receptor status in publication ____ supported by PHS funds	From the available research and medical records, the Committee was unable to confirm or refute the published result.	There was insufficient evidence to conclude that Respondent engaged in research misconduct on this issue.
Pt. Y was randomized into a clinical trial for breast cancer treatment for which she was not eligible	that Respondent falsified the eligibility checklist submitted to the data coordinating center by reporting that only a single tumor was present	From the medical records, including Respondent's charts and records from a second opinion consultation, the Committee determined that Respondent did not accurately report the patient's status to the data coordinating center.	By a preponderance of the evidence, including the Respondent's testimony, Respondent's actions constituted scientific misconduct by Respondent falsely reporting the presence of only a single tumor.
Pt Z was randomized into a clinical trial utilizing a potentially hepatotoxic drug without establishing her eligibility	that respondent falsified the claim for Pt Z's eligibility for the trial	The committee determined that baseline liver function tests (LFT's) required by the protocol had not been done. The center also determined that no LFT results were reported to the data coordinating center.	This was a protocol violation, but not a matter of falsification of records or results, and therefore Respondent's actions did not constitute scientific misconduct.